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Comparison of TNM staging systems for nasopharyngeal carcinoma, and proposal of a new staging system

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Background: There are few systematic evaluations regarding the sixth and seventh editions of the UICC/AJCC TNM Staging System (TNM6th, TNM7th) and Chinese 2008 Staging System (TNMc2008) for nasopharyngeal carcinoma (NPC).

Methods: We classified 2333 patients into intensity-modulated radiotherapy (IMRT) cohort ($n = 941$) and conventional radiotherapy (CRT) cohort ($n = 1392$). Tumour staging defined by TNM6th, TNM7th and TNMc2008 was compared based on Akaike information criterion (AIC) and Harrell's concordance index (c-index).

Results: For T-classification, TNM6th (AIC = 2585.367; c-index = 0.6390385) had superior prognostic value to TNM7th (AIC = 2593.242; c-index = 0.6226889) and TNMc2008 (AIC = 2593.998; c-index = 0.6237146) in the IMRT cohort, whereas TNMc2008 was superior (AIC = 5999.054; c-index = 0.623547) in the CRT cohort. For N-classification, TNMc2008 had the highest prognostic value in both cohorts (AIC = 2577.726, c-index = 0.6297874; AIC = 5956.339, c-index = 0.6533576). Similar results were obtained when patients were stratified by chemotherapy types, age and gender. Using staging models in the IMRT cohort, we failed to identify better stage migrations than TNM6th T-classification and TNMc2008 N-classification. We therefore proposed to combine these categories; resultantly, stage groups of the proposed staging system showed superior prognostic value over TNM6th, TNM7th and TNMc2008.

Conclusion: TNM6th T-classification and TNMc2008 N-classification have superior prognostic value in the IMRT era. By combining them with slight modifications, TNM criteria can be unified and its prognostic value be improved.

Nasopharyngeal carcinoma (NPC) is a non-lymphomatous, squamous-cell carcinoma that occurs in the epithelial lining of the nasopharynx. It has a distinct epidemiology, aetiology (Chang and Adami, 2006) and clinical manifestation (Wei and Sham, 2005) compared with other cancers, including other types of head and neck cancers. The highest rates of incidence occur in Southeast Asia, especially in Southern China, where the incidence of NPC can be as high as 20 to 30 per 100 000 (Cao *et al*, 2011). In contrast, NPC is relatively rare in Europe and the United States, where the incidence is only 0.5 to 2 per 100 000 (Ferlay *et al*, 2004).

An accurate staging system is critical for defining prognosis, determining appropriate treatment and evaluating treatment outcomes. The introduction of the sixth edition of the TNM staging system (TNM6th) for NPC (Greene *et al*, 2002), jointly adopted by the International Union against Cancer (UICC) and American Joint Committee for Cancer (AJCC), was an important landmark. Subsequent retrospective studies showed that nasal cavity/oropharynx involvement without parapharyngeal extension (T2a by TNM6th) had a similar, favourable prognosis to T1 (Lee *et al*, 2004; Liu *et al*, 2008; Mao *et al*, 2009); anatomic masticator

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space involvement including the medial and lateral pterygoid muscles had a similar prognosis to T4 (Tang *et al*, 2010); and retropharyngeal lymph node (RP-LN) metastasis, regardless of laterality, had a poorer prognosis than node-negative disease (Tang *et al*, 2008; Tham *et al*, 2009). Therefore, the recent seventh edition of the UICC/AJCC (TNM7th) (Edge *et al*, 2009, 2010) revised the criteria based on these findings. However, reverse evidence suggested that T2a patients should not be in the same prognostic group as T1 patients (Low *et al*, 2004); studies (Chua *et al*, 1997; Ng *et al*, 2007; Sun *et al*, 2013) revealed that RP-LN metastasis did not influence overall survival (OS) and distant metastasis-free survival (DMFS). In addition, with the enhanced locoregional control of intensity-modulated radiotherapy (IMRT), it needs a full reappraisal to see whether the prognosis of the medial and lateral pterygoid muscles involvement remains to be similar to T4. Finally, as NPC is especially prevalent in Southern China (Cao *et al*, 2011), the Chinese 2008 Staging System for NPC (TNMc2008) (CCSNPC, 2013) was released by the Chinese Committee for Staging of Nasopharyngeal Carcinoma, based on the Chinese 1992 Staging System.

Although TNM7th is now internationally recommended, TNMc2008 is widely used in the most endemic area – Mainland China. This discrepancy is because scientific evidence has not satisfactorily justified the use of these criteria in cancer staging. It greatly influences treatment assessment, and comparisons and clinical cooperation between different centres. Identification of the most useful staging criteria for therapeutic decision making is warranted. Few carefully designed studies have formally compared the two editions of UICC/AJCC staging system and the Chinese 2008 staging system to determine which is most useful for therapeutic decision making. Therefore, we performed this study to comprehensively evaluate and directly compare the three NPC staging systems – TNM6th, TNM7th and TNMc2008. In addition, considering the discrepancies between TNM6th, TNM7th and TNMc2008 and proposals from studies (Hu *et al*, 2010; Tang *et al*, 2010; Lee *et al*, 2012; Chen *et al*, 2012a,b; Li *et al*, 2013; Sun *et al*, 2013), we constructed staging models, compared them with the existing staging systems and ultimately proposed and confirmed some modifications for NPC staging system.

MATERIALS AND METHODS

Patients. The study was reviewed and approved by the Human Ethics Approval Committee at Sun Yat-sen University Cancer Center. We retrospectively reviewed the medical records of 2333 patients with newly diagnosed, biopsy-proven, non-metastatic NPC hospitalised at our centre. We classified them into three cohorts. The first one – IMRT cohort – involved 941 patients (714 men, 227 women; median age, 46 years; range, 13–84 years; histological type: I, 1; II, 35; and III, 905) treated with IMRT between January 2003 and December 2009. The second one – CRT cohort – involved 1392 patients (1054 men, 338 women; median age, 45 years; range, 12–80 years; type: I, 5; II, 70; and III, 1317) treated with conventional radiotherapy (CRT) between January 2005 and December 2006. To validate the results of the IMRT and CRT cohorts, we enrolled 1673 patients with NPC treated between January 2005 and December 2006, irrespective of radiation techniques, as the third cohort (1269 men, 404 women; median age, 45 years; range, 12–80 years; type: I, 6; II, 91; and III, 1576; IMRT, 281 (16.8%), CRT, 1392 (83.2%)).

All included patients had complete pretreatment evaluation including patient history, physical examination, haematology and biochemistry profiles, fiberoptic nasopharyngoscopy with biopsy, magnetic resonance imaging (MRI) of the nasopharynx and neck, chest radiography, abdominal sonography and Technetium-99m-methylene diphosphonate (Tc-99-MDP) whole-body bone scan. In addition, a total of 199 (8.5% of 2333) patients underwent 18F-fluorodeoxyglucose positron emission tomography and computed tomography (PET/CT) – 132 (14.0% of 941), 67 (4.8% of 1392) and 141 (8.4% of 1673) patients in the IMRT, CRT and the third cohort, respectively. Two radiologists independently reviewed all the images based on the MRI diagnosis criteria (see Supplementary Information) (King, 2010) and restaged all the patients according to the criteria of the three staging systems (Table 1). Any disagreements were resolved by consensus.

All patients were treated by definitive IMRT or CRT with or without chemotherapy; the radiation techniques and chemotherapy regimens have been described previously (Ma *et al*, 2007; Liang *et al*, 2009; Chen *et al*, 2012b). Considering the heterogeneous chemotherapy regimens, subgroup analysis by chemotherapy (induction chemotherapy (IC); concomitant chemotherapy (CC); IC plus CC; and CC plus adjuvant chemotherapy) was conducted in each cohort. In addition, stratified analysis by age and gender was also performed.

Patients were examined every 3–6 months during the first 3 years, with follow-up examinations every 6–12 months thereafter or until death. Patients without recent examination tests in the medical records were followed up by telephone call till June of this year. Within the median follow-up duration (from the first day of therapy) of 57 months (range, 3–124 months), 74 months (range, 2–102 months) and 74 months (range, 2–102 months) for the IMRT, CRT and the third cohort, 102 out of 941 (10.8%), 143 out of 1392 (10.3%) and 174 out of 1673 (10.4%) patients were lost to follow-up, with 200, 435 and 510 cases of treatment failure (locoregional relapse, distant metastasis or death from any cause, whichever was first; the diagnosing criteria were available in Supplementary Information), respectively.

Statistical analysis. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA) and R version 3.0.0 (www.r-project.org). Prognostic stratification of failure-free survival (FFS; time from the first day of therapy to the day of treatment failure) by T-classification, N-classification and clinical stage groups was evaluated using Akaike information criterion (AIC) (Akaike, 1973) and Harrell's concordance index (c-index) (Harrell *et al*, 1996). The AIC was analysed using Cox proportional hazards regression model with other prognostic covariates, including age (continuous), gender, histological type, chemotherapy type and radiation technique. The optimum model – the simplest effective model with the smallest information loss when predicting outcome – gives the lowest AIC value. Harrell's c-index was also calculated as a measure of predictive accuracy of survival outcome; a c-index of 0.5 indicates accuracy similar to random guessing, and that of 1.0 indicates 100% predictive accuracy. Actuarial FFS rates were estimated by the Kaplan–Meier method and survival curves were compared using the log-rank test. Multivariate analyses with covariates such as age and gender were used to calculate hazard ratios (HRs) by the Cox proportional hazards model. In addition, T-classification was included as a covariate in analyses of N-classification, and vice versa. Two-tailed *P*-values of <0.05 were considered statistically significant.

RESULTS

Comparison of the TNM6th, TNM7th and TNMc2008 staging systems. Generally speaking, the most obvious differences in T-classification among the three staging systems are the distributions of nasal cavity or oropharynx involvement, paranasal sinuses extension and medial and lateral pterygoid muscle involvement. With respect to N-classification, both TNM6th and TNM7th are graded according to the palpation-based greatest diameter of

Table 1. Classification criteria and stage groups by different systems for nasopharyngeal carcinoma

The 6th edition of UICC/AJCC	The 7th edition of UICC/AJCC	The Chinese 2008 staging system	The proposed staging system
T-classification			
T1: nasopharynx T2a: oropharynx and/or nasal cavity T2b: parapharyneal extension T3: bony structures and/or paranasal sinuses T4: intracranial extension and/or cranial nerves, infratemporal fossa hypopharynx, orbit or masticatory space[a]	T1: nasopharynx, oropharynx or nasal cavity T2: parapharyneal extension T3: bony structures and/or paranasal sinuses T4: intracranial extension and/or cranial nerves, hypopharynx, orbit or infratemporal fossa/masticatory space[b]	T1: nasopharynx T2: oropharynx, nasal cavity, parapharyneal extension T3: skull base, medial pterygoid muscle extension T4: cranial nerves, paranasal sinuses, masticatory space excluding medial pterygoid muscle, intracranial (cavernous sinus, dural meninges) extension	T1: nasopharynx T2: oropharynx, nasal cavity, parapharyneal extension, medial and lateral pterygoid muscles T3: bony structures and/or paranasal sinuses T4: intracranial extension and/or cranial nerves, infratemporal fossa hypopharynx, orbit or masticatory space excluding medial and lateral pterygoid muscles
N-classification			
N0: none N1: unilateral node(s), $\leqslant$6 cm in greatest dimension, above the supraclavicular fossa N2: bilateral node(s), $\leqslant$6 cm in greatest dimension, above the supraclavicular fossa N3a: $>$6 cm N3b: in supraclavicular fossa	N0: none N1: unilateral cervical and/or unilateral or bilateral retropharyngeal node(s), $\leqslant$6 cm in greatest dimension, above the supraclavicular fossa N2: bilateral cervical node(s), $\leqslant$6 cm in greatest dimension, above the supraclavicular fossa N3a: $>$6 cm N3b: in supraclavicular fossa	N0: none N1a: retropharyngeal node(s) N1b: unilateral level Ib, II, III and Va involvement, and the maximum diameter $\leqslant$3 cm N2: bilateral level Ib, II, III and Va involvement, or the maximum diameter $>$3 cm, or with extranodal neoplastic spread N3: level IV and Vb involvement	N0: none N1: unilateral or bilateral retropharyngeal node(s), unilateral level Ib, II, III, and Va involvement, and the maximum diameter $\leqslant$3 cm N2: bilateral level Ib, II, III and Va involvement, or the maximum diameter $>$3 cm, or with extranodal neoplastic spread N3: level IV and Vb involvement
Stage group			
I: T1 N0 M0 IIa: T2a N0 M0 IIb: T1-2a N1 M0, T2b N0-1 M0 III: T1-2b N2 M0, T3 N0-2 M0 IVa: T4 N0-2 M0 IVb: any T N3 M0 IVc: any T, any N M1	I: T1 N0 M0 II: T1 N1 M0, T2 N0-1 M0 III: T1-2 N2 M0, T3 N0-2 M0 IVa: T4 N0-2 M0 IVb: any T N3 M0 IVc: any T, any N M1	I: T1 N0 M0 II: T1 N1a-1b M0, T2 N0-1b M0 III: T1-2 N2 M0, T3 N0-2 M0 IVa: T1-3N3M0, T4 N0-3 M0 IVb: any T, any N M1	I: T1 N0 M0 II: T1 N1 M0, T2 N0-1 M0 III: T1-2 N2 M0, T3 N0-2 M0 IVa: T1-3N3M0, T4 N0-3 M0 IVb: any T, any N M1

Abbreviations: AJCC = American Joint Committee for Cancer; UICC = International Union against Cancer.
[a]Masticator space involvement denotes extension of tumour beyond the anterior surface of the lateral pterygoid muscle or lateral extension beyond the posterolateral wall of the maxillary antrum and the pterygomaxillary fissure.
[b]Masticator space primarily consists of the muscles of mastication. Anatomically, the superficial layer of the deep cervical fascia splits to enclose the muscles of mastication to enclose this space. These muscles are the medial and lateral pterygoid, masseter and temporalis.

tumour-positive lymph nodes, and TNM6th disregards RP-LNs, whereas TNMc2008 is classified using MRI-determined lymph node levels and sizes, extranodal neoplastic spread (ENS) and RP-LNs. In Supplementary Table 1, we have listed stage migration because of the differences among the three TNM systems for the IMRT and CRT cohorts. There were high proportions of N-classification changes ($>$20% cases) between TNM6th or TNM7th and TNMc2008, and $\sim$10% of cases had T-classification changes across the three systems.

The ability of each TNM staging system to stratify FFS is presented in Table 2. In the IMRT cohort, both AIC and c-index values revealed that TNM6th had superior prognostic value by T-classification (T1/T2/T3/T4), followed by TNMc2008 or TNM7th, whereas the prognostic value by N-classification (N0/N1/N2/N3) was highest for TNMc2008 followed by TNM7th and TNM6th. However, different trends were observed in the CRT cohort; TNMc2008 had superior prognostic value by both T-classification and N-classification, followed by TNM6th and then TNM7th. The results of the CRT cohort were validated in the third cohort. With regard to clinical stage group (I/II/III/IV), TNM6th had superior prognostic value in the IMRT cohort, followed by TNM7th and TNMc2008. In the CRT cohort, TNMc2008 was superior to TNM6th and TNM7th; this result was again validated in the third cohort.

In addition, we compared the prognostic value of the three staging systems in predicting FFS for the chemotherapy subgroups in each cohort. As shown in Table 3, in the IMRT cohort, the results of the RT alone set, CC set and IC plus CC set consistently demonstrated the highest prognostic value for T-classification of TNM6th and N-classification of TNMc2008, similar to the results obtained in the whole IMRT cohort. In the CRT cohort, the results of the RT alone set, IC set and CC set demonstrated the best prognostic value for T-classification and N-classification of TNMc2008, similar to the entire CRT cohort. However, in particular, in the IC plus CC set of the CRT cohort, the prognostic value of T-classification of TNM6th, rather than TNMc2008, was superior to the other staging systems, which was quite consistent with the results of the IMRT cohort. The N-classification of

Table 2. Comparison of TNM6th, TNM7th and TNMc2008 by the proportion of patient numbers allocated in each category and the prognostic value

	IMRT cohort (*N* = 941)					CRT cohort (*N* = 1392)					The third cohort (*N* = 1673)[a]				
Staging system	**No.**	**%**	**5-Year FFS (%)**	**AIC[b]**	**c-Index**	**No.**	**%**	**5-Year FFS (%)**	**AIC[b]**	**c-Index**	**No.**	**%**	**5-Year FFS (%)**	**AIC[b]**	**c-Index**
T-classification															
TNM6th				2585.367	0.6390385				6007.313	0.6140549				7232.252	0.6210207
T1	144	15.3	90.5			178	12.8	86.9			212	12.7	87.1		
T2a + T2b	231	24.6	84.4			377	27.1	77.8			452	27.0	79.1		
T3	397	42.2	75.6			530	38.1	68.2			638	38.1	68.8		
T4	169	18.0	60.6			307	22.1	59.7			371	22.2	59.2		
TNM7th				2593.242	0.6226889				6008.392	0.6137931				7236.528	0.6170047
T1	154	16.4	89.7			200	14.4	86.8			238	14.2	86.8		
T2	206	21.9	84.0			324	23.3	77.7			390	23.3	79.2		
T3	321	34.1	75.4			405	29.1	68.3			483	28.9	68.6		
T4	260	27.6	66.9			463	33.3	63.0			562	33.6	63.0		
TNMc2008				2593.998	0.6237146				5999.054	0.623547				7224.797	0.627451
T1	144	15.3	90.5			178	12.8	86.9			212	12.7	87.1		
T2	216	23.0	83.8			346	24.8	77.9			416	24.9	79.5		
T3	352	37.4	75.4			496	35.7	70.9			587	35.1	71.1		
T4	229	24.3	66.0			372	26.7	58.0			458	27.4	58.5		
N-classification															
TNM6th				2588.700	0.6051181				5997.412	0.6192496				7231.989	0.6541163
N0	291	30.9	86.0			346	24.9	85.1			439	26.2	84.9		
N1	396	42.1	76.5			642	46.1	70.6			755	45.1	70.7		
N2	206	21.9	74.5			308	22.1	65.1			368	22.0	66.5		
N3a + N3b	48	5.1	45.5			96	6.9	43.6			111	6.6	45.2		
TNM7th				2585.758	0.6071424				6000.594	0.6104974				7233.640	0.6544887
N0	199	21.1	89.1			241	17.3	86.4			308	18.4	86.5		
N1	488	51.9	76.9			747	53.7	72.4			886	53.0	72.2		
N2	206	21.9	74.6			308	22.1	65.1			368	22.0	66.5		
N3a + N3b	48	5.1	45.5			96	6.9	43.6			111	6.6	45.2		
TNMc2008				2577.726	0.6297874				5956.339	0.6533576				7181.886	0.6933172
N0	215	22.8	88.3			255	18.3	86.0			326	19.5	85.7		
N1a + N1b	413	43.9	78.8			583	41.9	76.7			694	41.5	76.8		
N2	235	25.0	73.5			434	31.2	64.5			517	30.9	65.0		
N3	78	8.3	51.6			120	8.6	38.7			136	8.1	38.6		
Stage group															
TNM6th				2563.425	0.6668522				5974.760	0.6385112				7187.989	0.6466896
I	74	7.9	92.8			71	5.1	94.3			89	5.3	94.3		
IIa + IIb	211	22.4	88.8			343	24.6	83.1			408	24.4	84.4		
III	445	47.3	78.3			595	42.7	70.8			715	42.7	71.3		
IVa + IVb	211	22.4	58.4			383	27.5	57.1			461	27.6	56.9		
TNM7th				2575.341	0.644973				5977.867	0.6383058				7196.383	0.6419891
I	64	6.8	94.9			67	4.8	92.5			84	5.0	92.8		
II	210	22.3	87.7			323	23.2	84.6			385	23.0	85.5		
III	373	39.6	77.9			470	33.8	70.9			562	33.6	71.6		
IVa + IVb	294	31.2	65.2			532	38.2	60.8			642	38.4	60.9		
TNMc2008				2592.678	0.651191				5950.440	0.6593581				7166.274	0.6618726
I	69	7.3	95.2			60	4.3	93.3			76	4.5	93.4		
II	184	19.6	87.1			274	19.7	87.3			329	19.7	88.0		
III	394	41.9	79.6			600	43.1	73.9			711	42.5	74.3		
IVa	294	31.2	63.9			458	32.9	55.4			557	33.3	56.0		

Abbreviations: AIC = Akaike information criterion; AJCC = American Joint Committee for Cancer; c-Index = Harrell's concordance index; CRT = conventional radiotherapy; FFS = failure-free survival; IMRT = intensity-modulated radiotherapy; TNM = tumour node metastasis; TNM6th = the sixth edition of the UICC/AJCC TNM staging system; TNM7th = the seventh edition of the UICC/AJCC TNM staging system; TNMc2008 = the Chinese 2008 Staging System for nasopharyngeal carcinoma; UICC = International Union against Cancer.

[a]The third cohort involved 1673 patients from January 2005 to December 2006, consisting of 281 out of 1673 (16.8%) patients with IMRT and 1392 out of 1673 (83.2%) with CRT treatment.

[b]The AIC was calculated in Cox proportional hazards regression model with age (continuous), gender, histological type and types of chemotherapy for the IMRT and CRT cohort, and also with radiation techniques for the third cohort.

Table 3. Comparison of TNM6th, TNM7th and TNMc2008 in predicting failure-free survival in subgroups of chemotherapy

	IMRT cohort (*N* = 941)		CRT cohort (*N* = 1392)		The third cohort (*N* = 1673)[a]	
Subgroups	**AIC [b]**	**c-Index**	**AIC[b]**	**c-Index**	**AIC[b]**	**c-Index**
RT alone set	(*n* = 219)		(*n* = 328)		(*n* = 396)	
T-classification						
TNM6th	303.375	0.6878003	901.218	0.6621048	1050.234	0.6715685
TNM7th	305.081	0.6824811	900.059	0.6754977	1048.985	0.6806435
TNMc2008	304.234	0.6817948	896.791	0.6757416	1046.935	0.6819199
N-classification						
TNM6th	297.935	0.6708991	901.584	0.6428327	1047.189	0.6559189
TNM7th	294.478	0.6914036	901.148	0.6381977	1047.472	0.6471761
TNMc2008	291.221	0.7268360	884.548	0.6748634	1027.730	0.6870432
IC set	None		(*n* = 281)		(*n* = 281)	
T-classification						
TNM6th	—	—	1083.046	0.5527778	1083.046	0.5527778
TNM7th	—	—	1083.147	0.5549505	1083.147	0.5549505
TNMc2008	—	—	1082.190	0.5685369	1082.190	0.5685369
N-classification						
TNM6th	—	—	1075.827	0.5958746	1075.827	0.5958746
TNM7th	—	—	1075.021	0.5921342	1075.021	0.5921342
TNMc2008	—	—	1061.585	0.6544279	1061.585	0.6544279
CC set	(*n* = 469)		(*n* = 423)		(*n* = 526)	
T-classification						
TNM6th	1187.584	0.5851499	1380.940	0.6128575	1771.414	0.6162836
TNM7th	1189.337	0.5762542	1380.908	0.6148377	1770.971	0.6175654
TNMc2008	1191.628	0.5601325	1376.665	0.6290704	1768.39	0.6269293
N-classification						
TNM6th	1178.929	0.5946466	1383.465	0.6110286	1775.976	0.5966301
TNM7th	1179.393	0.5852701	1383.542	0.5968647	1777.221	0.5876845
TNMc2008	1174.637	0.6141743	1381.203	0.6186331	1770.424	0.6183843
IC + CC set	(*n* = 186)		(*n* = 309)		(*n* = 414)	
T-classification						
TNM6th	489.122	0.6492647	1291.418	0.5798540	1737.786	0.5925196
TNM7th	493.670	0.6107353	1294.298	0.5564794	1742.804	0.5630775
TNMc2008	491.357	0.6338971	1292.766	0.5727775	1739.083	0.5865056
N-classification						
TNM6th	497.512	0.52352941	1286.780	0.5974569	1739.399	0.5786084
TNM7th	497.515	0.52294118	1288.125	0.5870632	1740.434	0.5711631
TNMc2008	495.107	0.55088240	1270.375	0.6623397	1723.176	0.6351195

Abbreviations: AIC = Akaike information criterion; AJCC = American Joint Committee for Cancer; CC = concomitant chemotherapy; c-Index = Harrell's concordance index; CRT = conventional radiotherapy; IC = induction chemotherapy; IMRT = intensity-modulated radiotherapy; RT = radiotherapy; TNM = tumour node metastasis; TNM6th = the sixth edition of the UICC/AJCC TNM staging system; TNM7th = the seventh edition of the UICC/AJCC TNM staging system; TNMc2008 = the Chinese 2008 Staging System for nasopharyngeal carcinoma; UICC = International Union against Cancer.

[a]The third cohort involved 1673 patients from January 2005 to December 2006, consisting of 281 out of 1673 (16.8%) patients with IMRT and 1392 out of 1673 (83.2%) with CRT treatment.

[b]The AIC was calculated in Cox proportional hazards regression model with age (continuous), gender and histological type for the IMRT and CRT cohort, and also with radiation techniques for the third cohort. However, AIC and c-Index were not calculated in the RT plus CC and adjuvant chemotherapy set because of limited number of patients ($n = 67$ in the IMRT cohort; $n = 51$ in the CRT cohort).

TNMc2008 still had the most favourable prognostic value in the IC plus CC set of the CRT cohort. When analysed by the multiple chemotherapy subgroups, the third cohort validated the results of the CRT cohort.

In the stratums by age ($\leqslant 60$ and > 60 years old) and gender, the results of comparison were quite similar to those in the overall cohort, respectively (Table 4).

Comparison of staging models. Given the above differences between patients treated with IMRT and CRT, and the recent recommendation of IMRT as the standard treatment by the Head and Neck Cancers of the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (Version 2, 2013; www.nccn.org), we constructed 10 T-classification models and 4 N-classification models with the 941 patients in the IMRT

Table 4. Comparison of TNM6th, TNM7th and TNMc2008 in predicting failure-free survival in stratified analysis by age (⩽60 and >60 years old) and gender

	IMRT cohort (*N* = 941)		CRT cohort (*N* = 1392)		The third cohort (*N* = 1673)[a]	
Stratums	**AIC[b]**	**c-Index**	**AIC[b]**	**c-Index**	**AIC[b]**	**c-Index**
Age ⩽60 years old	(*n* = 824)		(*n* = 1234)		(*n* = 1480)	
T-classification						
TNM6th	2003.721	0.6325691	4908.478	0.6122992	5806.033	0.6209916
TNM7th	2010.644	0.6175336	4917.419	0.6090601	5810.901	0.6141826
TNMc2008	2009.290	0.6212674	4907.862	0.6194509	5798.277	0.6265544
N-classification						
TNM6th	2004.321	0.6239475	4901.345	0.6239475	5804.875	0.6207027
TNM7th	2003.707	0.6172813	4903.039	0.6172813	5806.357	0.6149654
TNMc2008	1993.638	0.6658321	4854.533	0.6658321	5756.629	0.658327
Age >60 years old	(*n* = 117)		(*n* = 158)		(*n* = 193)	
T-classification						
TNM6th	368.177	0.6676618	712.375	0.6245186	932.624	0.6293492
TNM7th	369.362	0.6462916	710.596	0.634387	931.752	0.6357388
TNMc2008	371.565	0.6296354	710.525	0.6413671	930.872	0.6368664
N-classification						
TNM6th	375.870	0.6239475	712.66	0.6046213	934.879	0.5883806
TNM7th	372.357	0.6090601	714.124	0.5864891	935.447	0.5795747
TNMc2008	372.336	0.6658321	711.049	0.614249	928.596	0.627631
Male	(*n* = 714)		(*n* = 1054)		(*n* = 1269)	
T-classification						
TNM6th	2120.131	0.6392201	4701.974	0.6142803	5665.205	0.6212674
TNM7th	2124.745	0.6278203	4702.009	0.6141995	5668.907	0.6175336
TNMc2008	2126.928	0.6222739	4690.542	0.628093	5656.800	0.6325691
N-classification						
TNM6th	2118.398	0.6239475	4695.677	0.6200693	5666.261	0.6170331
TNM7th	2114.491	0.6172813	4699.371	0.6098774	5666.916	0.6100415
TNMc2008	2107.173	0.6658321	4660.241	0.6546294	5626.74	0.6522923
Female	(*n* = 227)		(*n* = 338)		(*n* = 404)	
T-classification						
TNM6th	299.740	0.6435911	917.401	0.6128287	1071.017	0.6334405
TNM7th	303.410	0.6036224	918.139	0.6116616	1071.860	0.6270442
TNMc2008	300.965	0.6340996	919.291	0.6050162	1072.319	0.6283753
N-classification						
TNM6th	304.453	0.6239475	913.893	0.6180926	1072.667	0.606749
TNM7th	305.631	0.6172813	914.196	0.6135194	1073.871	0.5981399
TNMc2008	304.022	0.6658321	907.748	0.6448647	1063.371	0.6396812

Abbreviations: AIC = Akaike information criterion; AJCC = American Joint Committee for Cancer; c-Index = Harrell's concordance index; CRT = conventional radiotherapy; IMRT = intensity-modulated radiotherapy; TNM = tumour node metastasis; TNM6th = the sixth edition of the UICC/AJCC TNM staging system; TNM7th = the seventh edition of the UICC/AJCC TNM staging system; TNMc2008 = the Chinese 2008 Staging System for nasopharyngeal carcinoma; UICC = International Union against Cancer.

[a]The third cohort involved 1673 patients from January 2005 to December 2006, consisting of 281 out of 1673 (16.8%) patients with IMRT and 1392 out of 1673 (83.2%) with CRT treatment.

[b]The AIC was calculated in Cox proportional hazards regression model with histological type, types of chemotherapy and age (continuous) or gender for the IMRT and CRT cohort, and also with radiation techniques for the third cohort.

cohort. The main changes of classification criteria from the based staging systems to our staging models were as follows (Supplementary Table 2). For T-classification, the first model (model-Ta1) downstaged oropharynx and/or nasal cavity involvement in TNM6th to T1, and the second (model-Ta2) downstaged oropharynx and/or nasal cavity involvement in TNMc2008 to T1. The third (model-Tb) classified oropharynx, nasal cavity and parapharyngeal extension as T1 *vs* TNM6th. The forth (model-Tc1) and fifth (model-Tc2) categorised paranasal sinus involvement as T4 *vs* TNM6th, and as T3 *vs* TNMc2008, respectively. The sixth (model-Td1) defined lateral pterygoid muscle involvement as T4 *vs* TNM6th, the seventh (model-Td2) defined it as T3 *vs* TNM6th and the eighth (model-Td3) defined it as T3 *vs* TNMc2008. The ninth (model-Te1) defined medial pterygoid

Table 5. Comparison of TNM6th and TNMc2008 staging models and the proposed staging system in predicting failure-free survival of 941 patients in the intensity-modulated radiotherapy cohort

		T-classification		N-classification		Stage group	
	Based staging system	AIC[a]	c-Index	AIC[a]	c-Index	AIC[a]	c-Index
Staging systems							
TNM6th		2585.367	0.6390385	2588.700	0.6051181	2563.425	0.6668522
TNMc2008		2593.998	0.6237146	2577.726	0.6297874	2592.678	0.6511910
Staging models							
Model-Ta1	TNM6th	2585.953	0.6381613	—	—	—	—
Model-Ta2	TNMc2008	2594.378	0.6229049	—	—	—	—
Model-Tb	TNM6th	2590.548	0.6304656	—	—	—	—
Model-Tc1	TNM6th	2588.819	0.6344470	—	—	—	—
Model-Tc2	TNMc2008	2592.163	0.6270070	—	—	—	—
Model-Td1	TNM6th	2590.323	0.6299291	—	—	—	—
Model-Td2	TNM6th	2585.388	0.6382018	—	—	—	—
Model-Td3	TNMc2008	2589.175	0.6320108	—	—	—	—
Model-Te1	TNM6th	2590.558	0.6260628	—	—	—	—
Model-Te2	TNM6th	2587.092	0.6348819	—	—	—	—
Model-Na	TNMc2008	—	—	2582.810	0.6203779	—	—
Model-Nb	TNMc2008	—	—	2600.696	0.6262281	—	—
Model-Nc	TNMc2008	—	—	2601.425	0.6271457	—	—
Model-Nd	TNMc2008	—	—	2601.719	0.6226484	—	—
The proposed staging system		2585.367	0.6390385	2577.726	0.6297874	2557.782	0.6707051

Abbreviations: AIC = Akaike information criterion; AJCC = American Joint Committee for Cancer; c-Index = Harrell's concordance index; TNM = tumour node metastasis; TNM6th = the sixth edition of the UICC/AJCC TNM staging system; TNMc2008 = the Chinese 2008 Staging System for nasopharyngeal carcinoma; UICC = International Union against Cancer.
[a]The AIC was calculated in Cox proportional hazards regression model with age (continuous), gender, histological type and types of chemotherapy.

muscle involvement as T4 *vs* TNM6th, and the last (model-Te2) defined it as T3 *vs* TNM6th. For N-classification, all four models were based on TNMc2008. The first (model-Na) classified positive RP-LN as stage N0, the second (model-Nb) disregarded ENS, the third (model-Nc) disregarded the size of positive cervical lymph nodes and the last (model-Nd) disregarded both ENS and cervical lymph node size.

The prognostic value of the 10 staging models for predicting FFS compared with the corresponding based TNM staging systems is presented in Table 5. For T-classification, both AIC and c-index revealed the poorer prognostic value of model-Ta1 *vs* TNM6th, model-Ta2 *vs* TNMc2008, and model-Tb *vs* model-Ta1; model-Tc1 was inferior to TNM6th, but model-Tc2 was superior to TNMc2008. In addition, the prognostic value of model-Td1 *vs* TNM6th and model-Td2 *vs* TNM6th was lower, but model-Td3 was superior to TNMc2008. Finally, both model-Td1 and model-Td2 were inferior to TNM6th. For N-classification, all models (model-Na, model-Nb, model-Nc and model-Nd) had a poorer prognostic value than TNMc2008, and model-Nd was inferior to both model-Nb and model-Nc.

The proposed staging criteria. The above staging models failed to lead to superior stage migrations with reference to T-classification of TNM6th and N-classification of TNMc2008, and actually revalidated the superiority of these aspects of the two TNM staging systems. We therefore proposed to combine the T-classifications of the TNM6th and N-classifications of the TNMc2008 with slight modifications (merging category T2a and T2b into T2, and category N3a and N3b into N3). (Table 1)

As indicated by the smaller AIC and larger c-index values, the clinical stage groups of the proposed staging criteria had superiority for predicting FFS in patients treated with IMRT compared with those of both TNM6th and TNMc2008 (Table 5). This observation was generally supported by the FFS curves ($P_{trend}<0.001$) and independent significance in multivariate analysis (adjusted HR 2.14, 95% CI 1.76–2.59, $P<0.001$), despite the nonsignificant increases in risk of failure between certain adjacent staging categories (stage I *vs* II: the log-rank test $P=0.069$; adjusted HR 3.07, 95% CI 0.91–10.34, $P=0.070$; Figure 1C and Table 6). Specifically, for T-classification and N-classification categories, the proposed staging criteria showed to be significant predictor for FFS in univariate and multivariate analyses (T-classification: the log-rank test $P_{trend}<0.001$; adjusted HR 1.63, 95% CI 1.38–1.92, $P<0.001$; N-classification: the log-rank test $P_{trend}<0.001$; adjusted HR 1.72, 95% CI 1.47–2.02, $P<0.001$). When evaluating T-classification and N-classification as categorical variables, unfortunately, we observed no significant segregations of T1 *vs* T2 ($P=0.063$, Figure 1A) and N1 *vs* N2 ($P=0.089$, Figure 1B).

DISCUSSION

A recent study (Pan *et al*, 2013) compared TNMc2008 with TNM7th in 816 Chinese patients from a single hospital. However, only 293 (35.9%) patients underwent IMRT and there were no stratification analyses according to radiation techniques, as there was significant higher local control rate using IMRT than CRT (Lai *et al*, 2011). Secondly, the most recent revision of TNM7th (Edge *et al*, 2010; King, 2010; Sun *et al*, 2013) was not applied properly, as medial and lateral pterygoid muscle involvement were not classified as T4. Moreover, unfortunately, the data set was so heterogeneous – with a wide range of treatments, in particular the

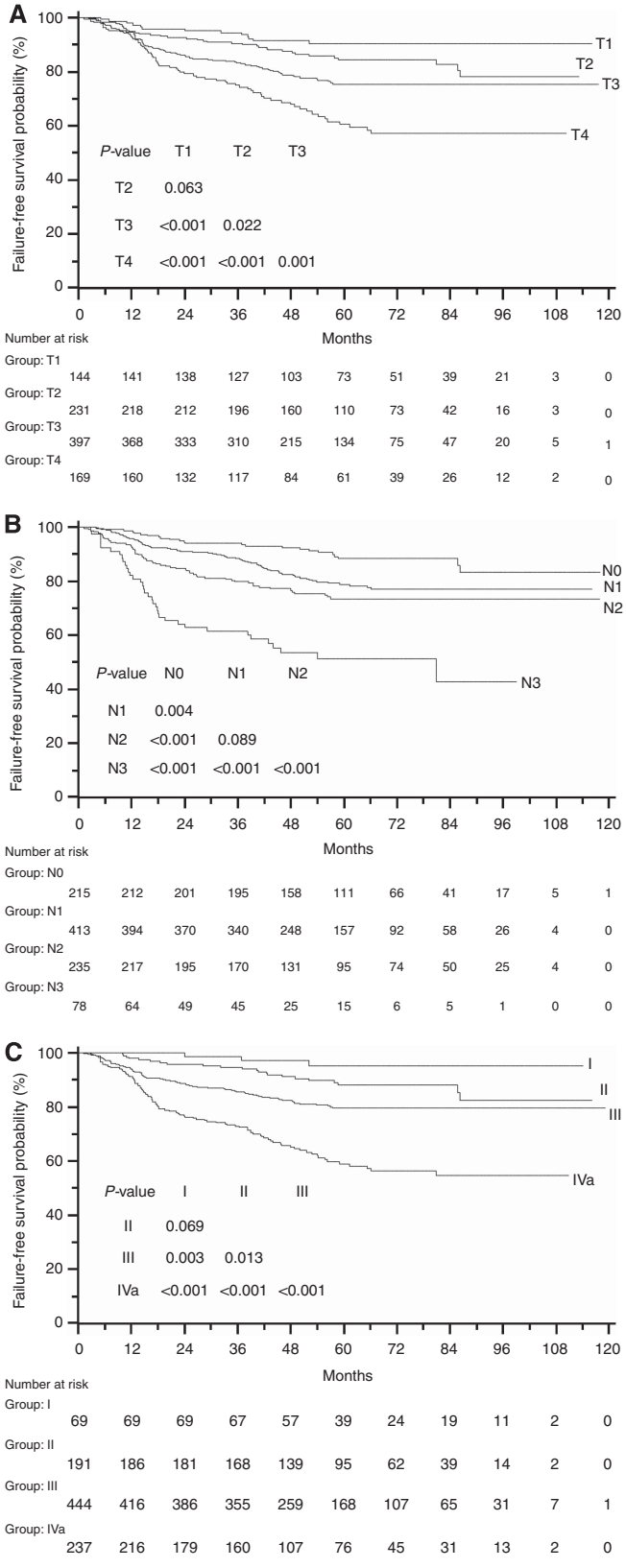

Figure 1. Failure-free survival of 941 patients in the intensity-modulated radiotherapy cohort according to the novel proposed staging system by (**A**) T-classification, (**B**) N-classification and (**C**) clinical stage group.

types of chemotherapy – that credible conclusions were hard to draw without stratification analyses or Cox regression analyses. Lastly and most importantly, survival curves were delineated by T- or N-classification of the respective staging systems, the classification categories were compared using the log-rank test and then the superiority of a staging system was judged on the basis of significant separations of the curves. In fact, survival curves are significantly affected not only by stage classification itself, but also by prognostic factors such as the treatment approach (IMRT *vs* CRT (Zhang *et al*, 2009; Lai *et al*, 2011; Peng *et al*, 2012), no chemotherapy *vs* chemotherapy and the type of chemotherapy (Baujat *et al*, 2006; OuYang *et al*, 2013)). Therefore, it is insufficient to determine which staging system has the highest prognostic value based on survival curves in terms of T- or N- stages alone, without considering other prognoses.

In contrast, in this study we enrolled a large number of MRI-based patients ($n=2333$), tested the staging systems in both the IMRT cohort ($n=941$) and CRT cohort ($n=1392$) and further validated the results in 1673 patients who were treated with either IMRT or CRT between 2005 and 2006 (Table 2). Secondly, we stratified the patients in each cohort by the major types of chemotherapy to eliminate the effects of chemotherapy heterogeneity (Table 3). In addition, stratified analysis on the patients' characteristics, such as age and gender, was also performed (Table 4). In essence, all staging systems are mathematical models for use in the clinic, and their ability to correctly predict patient survival must be evaluated as a whole, rather than be partially assessed based on the magnitude of segregation of each stage or category, as in previous studies (Liu *et al*, 2008; Mao *et al*, 2009; Lee *et al*, 2012; Chen *et al*, 2012b; Pan *et al*, 2013; Sun *et al*, 2013). Here, we scored the models according to their accuracy for predicting FFS in the same patients, and finally determined the superiority of the models – staging systems – according to AIC and c-index scores. In addition, patient characteristics, such as age and gender, were included in the calculation of AIC by Cox regression. Hence, our comparison of the staging systems is distinct to previous comparisons (Lee *et al*, 2012; Chen *et al*, 2012b; Pan *et al*, 2013; Sun *et al*, 2013), and more accurately and fully indicates the superiority of T-classification in TNM6th for IMRT patients, T-classification in TNMc2008 for CRT patients and N-classification in TNMc2008 for all patients.

Considering previous controversial findings regarding the prognosis of certain structure features in TNM staging criteria, it is not unexpected to observe insignificant improvement of TNM7th over TNM6th or TNMc2008. Also, we further validated the results by staging models.

For the T-classification categories, previous studies (Lee *et al*, 2004; Liu *et al*, 2008; Mao *et al*, 2009) found no significant differences in locoregional relapse-free survival (LRFS) between oropharynx and/or nasal cavity involvement and tumours confined to the nasopharynx; however, the poorer prognostic values of model-Ta1 *vs* TNM6th and model-Ta2 *vs* TNMc2008 suggest these features should not be categorised as stage T1, which is supported by the report from Low *et al* (2004). A recent study (Lee *et al*, 2012) even proposed downstaging of parapharyngeal extension to T1, but this recommendation was not supported by comparison of model-Ta1 with model-Tb. Another study (Tang *et al*, 2010) concluded that anatomic masticator space involvement including the medial and lateral pterygoid muscles should be classified as stage T4, despite the fact that anatomic masticator space involvement was a significant independent prognostic factor for OS ($P=0.02$), but not LRFS ($P=0.05$) or DMFS in the same study. Our staging models (model-Td1, model-Td2, model-Td3, model-Te1 and model-Te2) also failed to improve prognostic value when pterygoid muscles involvement was classified as stage T4 or T3. In addition, there are discrepancies in categorising the paranasal sinuses between the UICC/AJCC and Chinese staging systems, but no studies had compared the prognostic value of this feature with other structures involved in T4. For the first time, model-Tc1 and model-Tc2 support the classification of paranasal sinus

Table 6. Independent significance of T-classification, N-classification and stage group of the proposed staging system in predicting failure-free survival of 941 patients in the intensity-modulated radiotherapy cohort in multivariate analyses[a]

	T-classification			N-classification			Stage-group		
Covariates	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age (continuous)	1.019	1.006–1.031	0.003	1.020	1.008–1.033	0.002	1.018	1.006–1.031	0.003
Gender	0.491	0.331–0.729	<0.001	0.490	0.330–0.727	<0.001	0.513	0.346–0.762	0.001
Histological type	1.315	0.551–3.142	0.537	1.363	0.570–3.258	0.486	1.567	0.654–3.753	0.314
Chemotherapy	1.015	0.928–1.110	0.740	1.003	0.916–1.098	0.943	1.012	0.923–1.109	0.799
T-classification				1.648	1.389–1.956	<0.001			
T1 ($n=144$, 15.3%)	1.000			—	—	—	—	—	—
T2 ($n=231$, 24.5%)	1.391	0.731–2.647	0.315	—	—	—	—	—	—
T3 ($n=397$, 42.2%)	2.245	1.238–4.070	0.008	—	—	—	—	—	—
T4 ($n=169$, 18.0%)	3.838	2.076–7.094	<0.001	—	—	—	—	—	—
N-classification	1.718	1.458–2.024	<0.001						
N0 ($n=215$, 22.8%)	—	—	—	1.000			—	—	—
N1 ($n=413$, 43.9%)	—	—	—	1.725	1.086–2.742	0.021	—	—	—
N2 ($n=235$, 25.0%)	—	—	—	2.165	1.335–3.509	0.002	—	—	—
N3 ($n=78$, 8.3%)	—	—	—	6.173	3.627–10.507	<0.001	—	—	—
Stage group									
I ($n=69$, 7.3%)	—	—	—	—	—	—	1.000		
II ($n=191$, 20.3%)	—	—	—	—	—	—	3.074	0.914–10.341	0.070
III ($n=444$, 47.2%)	—	—	—	—	—	—	5.365	1.661–17.330	0.005
IVa ($n=237$, 25.2%)	—	—	—	—	—	—	12.066	3.705–39.292	<0.001

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a]The T-classification was included as a covariate in analyses of the N-classification, and vice versa.

involvement as T3. In brief, our staging models for the T-classification category present concrete evidence of the advantages of T-classification in TNM6th without the new regrouping suggestions. The following reasons may explain the nonsignificant prognostic values of our models in contrast to previous studies (Lee *et al*, 2004; Liu *et al*, 2008; Mao *et al*, 2009; Tang *et al*, 2010; Lee *et al*, 2012). Firstly, there were a limited number of cases with solely oropharynx and/or nasal cavity involvement; therefore, based only on the magnitude of segregation of the survival curves by the log-rank test (Lee *et al*, 2004; Liu *et al*, 2008; Mao *et al*, 2009), significant differences were difficult to observe between these cases and those with tumours confined to the nasopharynx when both groups have such high survival rates. However, the slight differences between our models and TNM6th or TNMc2008 could be detected using the AIC and c-index values. Secondly, as IMRT provides better locoregional control than CRT (Zhang *et al*, 2009; Lai *et al*, 2011; Peng *et al*, 2012), it is reasonable that categorisation of the medial and lateral pterygoid muscles and paranasal sinuses as stage T4 did not improve prognostic values. The enhanced locoregional control offered by IMRT may also explain the phenomenon that TNM6th had the best prognostic value in the IMRT cohort, whereas TNMc2008 was superior in the CRT cohort and third cohort (Table 2). Furthermore, it is possible that the combination of IC plus CC and RT leads to an extremely high survival rate (Hui *et al*, 2009), which may explain why TNM6th, rather than TNMc2008, had superior prognostic value in the IC plus CC sets of the CRT cohort and third cohort (Table 3). Because of the small proportion of patients (16.8%) treated with IMRT in the third cohort, its results were quite consistent with those of the CRT cohort.

For the N-classification categories, the MRI-based TNMc2008 was superior to the other systems as a whole, similar to the results of a previous study (Pan *et al*, 2013). This result was not unexpected, considering that the palpation-based greatest dimension in TNM6th and TNM7th might contain subcutaneous tissues, and the fact that differences between clinicians and their characterisation of palpated tumours can result in chaotic diversity in prognostic assessment (Lee *et al*, 1996; Heng *et al*, 1999). Because of the uncertain prognostic value of RP-LN in previous studies (Chua *et al*, 1997; Lu *et al*, 2006; Ma *et al*, 2007; Ng *et al*, 2007; Tang *et al*, 2008; Tham *et al*, 2009; Sun *et al*, 2013), we constructed the TNMc2008-based model-Na, and proved the importance of classifying positive RP-LN as N1. Secondly, because of the contradictory prognostic value of ENS in two studies (Mao *et al*, 2008; Li *et al*, 2013), we constructed model-Nb, and found that ENS involvement should be classified as N2. In addition, the significance of cervical lymph node size determined by clinical palpation (Lee *et al*, 1996; Heng *et al*, 1999) or MRI (Mao *et al*, 2008; Li *et al*, 2013) remained unclear; therefore, we constructed model-Nc, which demonstrated that lymph node size should not be disregarded in N-classification. In addition, the significant roles of ENS and lymph node size were revalidated by the poorer prognostic value of model-Nd as compared with model-Nb and model-Nc, which opposes the proposed N-classification system by Li *et al* (2013). In summary, our staging models for the N-classification categories provided concrete evidence for the advantages of N-classification in TNMc2008 without the new regrouping suggestions.

Based on our comparison of TNM6th, TNM7th and TNMc2008, and the results of the staging models, we proposed to combine T-classification of TNM6th and N-classification of

TNMc2008 (Table 1). The proposed staging system criteria led to a balanced clinical stage group distribution, and its clinical stage group had obviously superior prognostic value over TNM6th, TNM7th and TNMc2008 (Table 5), although no significant separation of risk of failure was observed between stage I and II ($P = 0.069$, Figure 1C; $P = 0.070$, Table 6).

The following limitations of this study deserve comment. Firstly, despite carefully designed step-by-step comparisons, this study was conducted on the basis of retrospective analysis of a large number of cases from a single centre; apart from 281 (16.8%) patients from the IMRT cohort, the validation (third) cohort consisted of all the same patients in the CRT cohort, instead of the other totally different population of patients. Therefore, the results of comparing the three staging systems and especially the prognostic value of the proposed staging system need to be further confirmed in a prospective multicentre clinical study. This is what we are planning at the moment. Secondly, because the RT techniques influenced the prognostic values of T-classification, and IMRT is now recommended for NPC, our proposed staging system was constructed and validated based on cases treated with IMRT; therefore, the T-classification and clinical stage groups of the proposed staging system may not be applicable to patients treated with CRT. Thirdly, there were nonsignificant segregations between certain adjacent stage categories using our proposed staging system. The small proportion of patients and low treatment failure rate in these stratums are important factors that should be considered. Also, this may be influenced by selection biases of patients. Further validations with data of patients from other centres are required. In addition, only the FFS was evaluated because of the large volume of data. But the events of FFS consist of locoregional relapse, distant metastasis or death, whichever is first. It is of excellence in reflecting the survival of patients, and commonly used as the primary end point in the recent randomised controlled trials. Finally, our proposed staging system had superior prognostic value over the three existing systems; unfortunately, it remains complicated. A simplified and superior staging system needs to be explored.

To summarise, TNM6th T-classification and TNMc2008 N-classification have superior prognostic value for patients treated with IMRT; TNMc2008 T-classification and N-classification were shown to be better than TNM6th and TNM7th for patients treated with CRT. In this study, TNM7th showed no significant improvement over TNM6th. In the IMRT era, combining TNM6th T-classification and TNMc2008 N-classification with slight modifications, we propose a new staging system: (1) T-classification: T1, nasopharynx; T2, oropharynx, nasal cavity, parapharyneal extension, medial and lateral pterygoid muscles; T3, bony structures and/or paranasal sinuses; T4, intracranial extension and/or cranial nerves, infratemporal fossa hypopharynx, orbit or masticatory space excluding medial and lateral pterygoid muscles; (2) N-classification: N0, none; N1, unilateral or bilateral retropharyngeal node(s), unilateral level Ib, II, III and Va involvement and the maximum diameter $\leqslant 3$ cm; N2, bilateral level Ib, II, III and Va involvement or the maximum diameter > 3 cm or with extranodal neoplastic spread; N3, level IV, Vb involvement; (3) stage group: I, T1N0M0; II, T1N1M0, T2N0-1M0; III, T1-2N2M0, T3N0-2M0; IVa, T1-3N3M0, T4N0-3M0; and IVb, any T any N M1. Thus, TNM classification for NPC can be unified internationally and its prognostic value improved.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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